II. REMARKS/ARGUMENTS

The present response is a substitute for the response filed on December 1, 2008. In accordance, with the Examiner's suggestion (as set forth in the Substance of Interview below), Applicants hereby state that the elected invention and the elected species are encompassed by claims 38, 47, 48, and 53-64.

A. Substance of Interview

Applicants hereby make of record the substance of telephone interview conducted on March 16, 2009, between the undersigned attorney and Examiner Christopher M. Gross.

During the Interview, the Examiner indicated that the Office Action mailed on March 4, 2009, was issued because it was not clear to the Examiner the elected species were included in the phrase "the elected invention" in the last sentence of the Status of the Claims section on page 5 of the response filed on December 1, 2008.

The undersigned attorney clarified that the elected species were included in this phrase.

Applicants thank the Examiner for the telephone interview and respectfully request that the substance of this interview be made of record.

B. Status of claims

Claims 1-37, 39-46 and 49-52 were previously canceled without prejudice.

Claims 63 and 64 have been added. Support for new claims 63 and 64 can be found, e.g., on page 20, line 31.

Claims 38, 47, 48, and 53-64 are currently pending.

Applicants respectfully submit that no new matter has been added by virtue of these amendments; and that the elected invention and the elected species are encompassed by claims 38, 47, 48, and 53-64.

C. Claim Rejections- 35 U.S.C. § 112, first paragraph

Claims 54 and 57 were rejected under 35 U.S.C. § 112, first paragraph. The Examiner stated that "the specification, while being enabling for treating pain associated with COX-1/2 receptors and/or opioid receptors, does not reasonably provide enablement for every type of pain" recited in claim 54. *Office Action, page 3.*

The rejection is respectfully traversed.

Claims 54 and 57 depend from claims 38 and 55. The Examiner has acknowledged that the subject matter of claims 38 and 55 is enabled by the present specification. *Id ("the specification ... [is] enabling for treating pain associated with COX-1/2 receptors and/or opioid receptors").* The scopes of claims 38 and 55 therefore do not extend beyond the scope of the specification. Accordingly, the scopes of claims 54 and 57 are also within the scope of the specification, because these claims depend from claims 38 and 55, which, as acknowledged by the Examiner, are enabled.

Applicants further submit that the methods of claims 54 and 57 can be practiced without undue experimentation, e.g., in view of the guidance provided by the specification. Independent claims 38 and 55 recite specific drugs and amounts to be administered in the methods of these claims. Claims 54 and 57 provides a non-limiting list of illnesses for which the specific drugs of claims 38 and 55 could be administered. It is respectfully submitted that one skilled in the art will be able to administer the specific drugs in the specific amounts recited in claims 38 and 55

to a patient diagnosed with one or more illness recited in claims 54 and 57 without undue experimentation.

In response to the Examiner's reliance on Wikipedia, Applicants note that according to the Board of Patent Appeals and Interferences Wikipedia "is considered unreliable because it is a source that "anyone" can edit." *Decision on Appeal, Appeal 2007-2450, page 5 (September 5, 2007).*

Applicants further contend the rejection is improper because six of the seven references relied upon by the Examiner in support of the rejection published after the effective filing date of the present application.

Withdrawal of the rejection is respectfully requested.

D. Claim Rejections- 35 U.S.C. § 103

Claims 38, 47, 48, 53, and 54 were rejected under 35 U.S.C. § 103(a) over Baker et al. (U.S. Patent No. 4,569,937) in view of Furst (Furst, D.E. "Meloxicam: Selective COX-2 inhibition in clinical practice" Seminars in Arthritis and Rheumatism, June 1997, 26(1), 21-27) and in further view of Oshlack I et al. (U.S. Patent No. 5,472,712) and/or Oshlack II (U.S. Patent No. 6,294,195) and Iyengar et al. (WO 97/25988), and as evidenced by Wikipedia if necessary (Wikipedia, the Free Encyclopedia. Meloxicam. Retrieved at on May 26, 2008 from http://en.wikipedia.org/wiki/Meloxicam, pages 1-3). *Office Action, page 8.*

The Examiner stated that "[i]t would have been *prima facie* obvious to one skilled in the art at the time of the invention was made to substitute Meloxicam as taught by the combined references of Furst, Oshlack I/II et al. and Iyengar et al. for the Ibuprofen in the ibuprofen/oxycodone compositions as taught by Baker et al," allegedly because melcoxicam "is

more potent ...[and] also because it is safer than other NSAIDs including the ibuprofen ..." *Office Action, page 15.*

This rejection is respectfully traversed, for the reasons given below and the reasons set forth in the previously filed responses.

Applicants respectfully submit that meloxicam is not an equivalent of ibuprofen, because the chemical structure, physical properties and pharmacokinetic parameters of meloxicam are different than those of ibuprofen. Further, the cited references do not teach that meloxicam is an equivalent of ibuprofen and do not provide a reason for substituting ibuprofen with meloxicam in the synergistic combination of the Baker reference, as demonstrated below.

In response to the Examiner's statement that "Meloxicam exhibits less serious gastric and renal side effects ...," Applicants note that "[t]he *Drug and Therapeutics Bulletin*, the British equivalent of our *Medical Letter*, which is sent to all British physicians, said in its August, 1998 issue that "There is no convincing evidence that the risk of the severest adverse gastrointestinal events, namely peptic ulceration, perforation and bleeding, is lower with meloxicam that with other NSAIDS when given at equ-effective doses ... Meloxicam has not been compared with ibuprofen ... which comes out best in most safety assessments." *Statement before the Food and Drug Administration's Arthritis Drugs Advisory Committee on the nonsteroidal anti-inflammatory drug celecoxib (HRG Publication #1465), December 1, 1998.*

Further, the FINAL DRAFT LABELING approved by the FDA on April 13, 2000, for Mobic® (meloxicam) stated regarding gastrointestinal effects of meloxicam:

> Serious gastrointestinal toxicity, such as inflammation, bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, can occur at any time, with or without warning symptoms, in patients treated with nonsteroidal anti-inflammatory drugs (NSAIDs). Minor upper gastrointestinal problems, such as dyspepsia, are common and may also occur at any time during NSAID therapy ....

Final Draft Labeling, NDA 20-938, page 4, April 13, 2000.[1]

The FINAL DRAFT LABELING did not therefore differentiate meloxicam from other NSAIDs (e.g., ibuprofen), e.g., as being a "safer" alternative to other NSAIDs. In fact, the medical review based on which Mobic ® (meloxicam) was approved inter alia stated that:

> The agency and the sponsor engaged in a series of labeling discussion centering on the nature of the meloxicam submission vis-à-vis the Cox 2 hypothesis that there may be a lower incidence of serious GI adverse events due to selective inhibition of COX2 rather than COX1 enzyme. It was the agency's position that there was insufficient pharmacology and endoscopy information to support a COX2 mechanism of action for Meloxicam. The sponsor also conducted a post hoc, combined analysis of serious GI adverse effects, but agency felt that the uncertainty in post hoc inferences could not justify their inclusion as labeling.

Medical Review, NDA 20-938, March 27, 2000.[2]

In other words on March 27, 2000, the FDA could not conclude, based on the data generated prior to March 27, 2000, that meloxicam had less serious GI adverse events than other NSAIDs (e.g., ibuprofen).

The Furst reference which is relied upon by the Examiner for the purported teaching that meloxicam is "more effective than other NSAIDs" and "exhibits less serious gastric and renal side effects than ibuprofen," lacks data comparing gastrointestinal side effects of ibuprofen and meloxicam. In response to the Examiner's statement that Table 2 shows "meloxicam to be the "safest" NSAID especially with regard to gastrointestinal effects," Applicants note that Table 2 does not contain any data for ibuprofen. The Furst reference therefore cannot establish that meloxicam is a safer alternative than ibuprofen, which, according to the 1998 Statement before the Food and Drug Administration's Arthritis Committee, "comes out best in most safety assessments."

[1] A copy of the FINAL DRAFT LABELING is being submitted in an Information Disclosure Statement which is being filed concurrently with the present response

[2] A copy of the Medical Review is being submitted in an Information Disclosure Statement which is being filed concurrently with the present response

The Examiner's assertions about the comparative safety and efficacy of meloxicam are therefore incorrect, because the cited references do not demonstrate that meloxicam is a safer drug than ibuprofen. In fact, as stated above, FDA could not conclude during regulatory review of Mobic® (meloxicam) that meloxicam had less serious GI adverse events than other NSAIDs (e.g., ibuprofen).

Regarding the Examiners reliance of Wikipedia, Applicants contend that this reliance is improper. *Decision on Appeal, Appeal 2007-2450, page 5 (September 5, 2007).*

The combination of the cited references does not therefore provide a reason for replacing ibuprofen with meloxicam in the synergistic combination of Baker reference. *See e.g., Statement before the Food and Drug Administration's Arthritis Drugs Advisory Committee on the nonsteroidal anti-inflammatory drug celecoxib (HRG Publication #1465), December 1, 1998 ("[t]here is no convincing evidence that the risk of the severest adverse gastrointestinal events, namely peptic ulceration, perforation and bleeding, is lower with meloxicam that with other NSAIDS when given at equ-effective doses ...").*

Withdrawal of the rejection is respectfully requested.

With regard to new claims 63 and 64, it is respectfully submitted that the cited references do not teach or suggest administering meloxicam twice-a-day.

Claims 38, 47, 48, 53-62 were rejected under 35 U.S.C. § 103(a) over Baker et al. (U.S. Patent No. 4,569,937) and Furst (Furst, D.E. "Meloxicam: Selective COX-2 inhibition in clinical practice" Seminars in Arthritis and Rheumatism, June 1997, 26(1), 21-27) and in further view of Oshlack I et al. (U.S. Patent No. 5,472,712) and/or Oshlack II (U.S. Patent No. 6,294,195) and Iyengar et al. (WO 97/25988), and further in view of Eichel et al. (U.S. Patent No. 5,376,384) and Miller et al. (EP 0649657), as evidenced by Wikipedia if necessary (Wikipedia, the Free

Encyclopedia. Meloxicam. Retrieved at on May 26, 2008 from http://en.wikipedia.org/wiki/Meloxicam, pages 1-3).

The rejection is respectfully traversed.

Applicants respectfully submit that that the cited references do not suggest substitution of ibuprofen with meloxicam for the reasons set forth above.

Regarding the Examiners reliance of Wikipedia, Applicants again contend that this reliance is improper. *Decision on Appeal, Appeal 2007-2450, page 5 (September 5, 2007).*

Withdrawal of the rejection is respectfully requested.

III. CONCLUSION

An early and favorable action on the merits is earnestly solicited. The Examiner is respectfully requested to contact the undersigned at the telephone number provided below in the event that a telephonic interview will advance the prosecution of the application.

Respectfully submitted,
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